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Letters to the Editor

The Role of Omega-3 Fatty Acids in Primary Prevention of Coronary Artery Disease and in Atrial Fibrillation Is Controversial

We read with interest a recent review article on the cardiovascular effects of omega-3 fatty acids (ω-3 PUFA) by Lavie et al. (1) and wish to highlight some of the controversial issues in this review. In relation to the role of ω-3 PUFA in primary prevention of coronary artery disease (CAD), the authors quote 3 studies—the DART (Diet And Reinfarction Trial) (2), GISSI Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico–Prevenzione) study (3), and JELIS (Japan EPA Lipid Intervention Study) (4)—as supportive evidence for a beneficial effect. As discussed further in the same review, the DART and GISSI Prevenzione studies are secondary prevention studies, and in the JELIS—which included 14,981 subjects in primary prevention and 3,664 subjects in secondary prevention—major coronary events were indeed significantly reduced in the ω-3 PUFA-treated subjects. However, when the groups with and without previous CAD (i.e., primary and secondary prevention cohorts) were individually analyzed, there was no benefit in the primary prevention group. Therefore, the 3 studies quoted by the authors do not lend any supportive evidence to the claim that ω-3 PUFA are useful in primary prevention of CAD.

In addition, the authors claim that the most significant antiarrhythmic effects of ω-3 PUFA are noted in studies on atrial fibrillation (AF) and quote 2 interventional studies (5,6) in addition to 1 observational study (7). To our knowledge, there has been only 1 interventional study published on the effect of ω-3 PUFA on AF after coronary artery bypass graft surgery. This study by Calò et al. (5) is a relatively small open-label study in 160 patients who received 2 g/day of ω-3 PUFA for 5 days before coronary artery bypass surgery. The second study referred to by the authors (6) is in fact a systematic review of studies that have evaluated all interventions that might be of benefit in reducing AF after coronary artery bypass graft surgery.

We wish to highlight that there were 2 large epidemiological studies—the Rotterdam Study (8) quoted by the authors and the Danish Diet, Cancer and Health study (9)—that showed no association between the risk of developing AF and dietary fish intake.

Of note, the study by Mozaffarian et al. (7) exclusively looked at subjects ≥65 years of age and could not be extrapolated to the entire population at risk of AF, which would include both young (often lone AF) and old (often with underlying structural heart disease).

The authors have failed to indicate that a recent systematic review by León et al. (10) and a systematic review of the 3 large studies on implantable cardioverter-defibrillator population (11) have reported no benefit with ω-3 PUFA therapy on cardiac arrhythmias. Hence, we believe that the role of ω-3 PUFA on primary prevention of CAD and AF are far from clear as this review seems to suggest.

***Palaniappan Saravanan, MD**
Neil C. Davidson, MD

*Cardiovascular Research Group
University of Manchester
46. Grafton Street
Manchester M13 9LT
United Kingdom
E-mail: palaniappan.saravanan@manchester.ac.uk

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Reply

We thank Drs. Saravanan and Davidson for their insightful comments regarding details of our omega-3 polyunsaturated fatty acid (ω-3 PUFA) review and appreciate the opportunity to clarify issues that might have been prone to misinterpretation (1). We did not imply that the DART (Diet and Reinfarction) study (2), GISSI Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico–Prevenzione) study (3) and JELIS study (Japan EPA Lipid Intervention Study) (4) were trials with a uniform population but in fact stated that they represent an aggregate of evidence toward both secondary and primary prevention. They correctly point out that the DART study (2) and the GISSI-Prevenzione study (3) are secondary prevention studies with a significant ω-3 PUFA benefit in over 13,000 post-myocardial infarction patients. However, even in secondary prevention, not all studies have demonstrated benefit (1). The JELIS trial (4), in contrast, tested the effects of eicosapentaenoic acid (EPA) in mostly a primary prevention cohort (n = 14,981 with hypercholesterolemia treated with statins). Here, the effect size was essentially identical (18% vs. 19%) to that seen in the secondary prevention group (n = 3,664), but the 5-year event rate was nearly 6-fold higher in the secondary prevention group (12% vs. < 2%). As Drs. Saravanan and Davidson correctly point out, in the entire primary prevention group, the benefits of EPA were not quite statistically significant (hazard ratio: 0.82; 95% confidence interval: 0.63 to 1.06; p = 0.13). In a subgroup of JELIS primary prevention patients (5), those with triglycerides ≥150 mg/dl and high-density lipoprotein cholesterol <40 mg/dl had event rates that were nearly 2-fold higher than those without this lipid pattern. In patients with this high-risk lipid combination, EPA reduced major cardiac event rates by 53% (p = 0.043). Along with the notable epidemiological data, we believe that the overall evidence suggests benefits of ω-3 PUFA at least in high-risk risk primary prevention patients as well as in those needing secondary prevention of coronary heart disease.

We agree with Drs. Saravanan and Davidson that our single, brief paragraph on the impact of ω-3 PUFA in atrial fibrillation (AF) was oversimplified (in an effort to make a lengthy review more concise). Although the observational study by Mozaffarian et al. (6) suggested that high fish intake was associated with a 30% reduction in AF over 12 years, the Rotterdam Study (7) found no such effect. Only 1 small randomized controlled study of 160 post-bypass patients was performed to assess the benefits of ω-3 PUFA on the development of postoperative AF (8). The results of this small study were remarkable in support of ω-3 PUFA, including 18.1% absolute risk reduction and 54.4% relative risk reduction (or only 5.5 patients needed to be treated to prevent 1 episode of AF). As this study points out and as we have discussed elsewhere in more detail (9), these results compare favorably to the results of another large meta-analysis (58 studies including 8,565 participants) (10), which examined the effects of amiodarone, sotalol, and beta blockers on post-bypass AF. In comparison, the results with ω-3 PUFA post-bypass seem to be similar or even superior to these other treatments to prevent AF. Clearly, larger studies are needed and some are underway (11) to assess the impact of ω-3 PUFA in primary and secondary prevention of AF. Additionally, higher doses of ω-3 PUFA (e.g., 2 to 5 g/day) need to be studied in various cardiovascular diseases (CVD), including AF, and studies are needed to determine the relative benefits of EPA and docosahexaenoic acid (DHA) in CVD. It also is not known what impact DHA or EPA alone has in disease modification, these areas being the subject of intense ongoing investigation.

Finally, we agree with Drs. Saravanan and Davidson that one could debate the details of the strengths and weaknesses of each study. However, we believe the totality of the evidence suggests an overall beneficial effect of ω-3 PUFA for CVD protection, a view that we are not alone in professing (12–14).

***Carl J. Lavie, MD**
Richard V. Milani, MD
Mandeep R. Mehra, MD
Hector O. Ventura, MD

*Ochsner Medical Center
Cardiovascular Diseases
1514 Jefferson Highway
New Orleans, Louisiana 70121
E-mail: clavie@ochsner.org

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